REMARKS

Claims 1-4, 6, 9-12, 14, and 23-26 are pending in this application. Claims 1-4, 6, 23, and 24 were rejected under 35 U.S.C. § 112, second paragraph. Claims 1-4, 6, 9-12, 14, and 23-26 were variously rejected under 35 U.S.C. § 112, first paragraph. Claims 1-4, 6, 9-12, 14, and 23-26 were rejected under 35 U.S.C. § 103.

By this amendment, claims 1 and 9 have been amended without prejudice or disclaimer of any previously claimed subject matter. Support for the amendments can be found, *inter alia*, throughout the specification, for example, at page 14, lines 18-21.

The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-4, 6, 23, and 24 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner states that "it is still unclear how the development of the symptoms can be delayed where the lesion is already present." Office Action, page 3. Applicants respectfully traverse this rejection.

As noted in the specification at page 15, delaying development of a viral infection or symptom of a viral infection means to defer, hinder, slow, retard, stabilize, and/or postpone development of the disease or symptom. Lesions associated with papillomavirus infection grow and

develop over time[1] and, clearly, a delay in the development of such a lesion would be desirable to the individual. Applicants respectfully submit that the claims are sufficiently definite when considered in view of the specification and the understanding of those of skill in the art.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-4, 6, 9-12, 14, and 23-26 were rejected under 35 U.S.C. §112, first paragraph, for allegedly not enabling any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention without undue experimentation. Claims 1-4, 6, 9-12, 14, and 23-26 were rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to comply with the written description requirement. Applicants respectfully traverse these rejections.

The Examiner acknowledges that "Applicant has demonstrated that the administration of an ISS to a papillomavirus-associated lesion results in a slowing of the development of the lesion" and that "Applicant has demonstrated that the administration of an ISS may reduce severity of a papillomavirus-associated lesion." However, for both the enablement and written description rejections the Examiner asserts that Applicants have "not demonstrated that the administration would result in the inhibition or reduction in severity of any symptom associated with the infection." Office Action, pages 3-4.

Solely to promote prosecution of this application and without acquiescing to these rejections, the claimed invention has herein been amended to a method of delaying development and to a method of reducing severity of a lesion associated with papillomavirus infection. Thus, the pending claims fall within the subject matter that is enabled and described by the specification.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §112, first paragraph.

[1] See, for example, Figures 2 and 3 of the specification.

Rejection under 35 U.S.C. § 103

Claims 1-4, 6, 9-12, 14, and 23-26 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Beutner *et al.* (1998, *J. Am. Acad. Dermatol.* 38:230-239, "Beutner"), Bauman *et al.* (1996, *Pediatr Clin. N. Am.* 43:1385-1401, "Bauman"), and Yamamoto *et al.* (1994, *Jpn. J. Cancer Res.* 85:775-779, "Yamamoto") and further in view of either of Raz *et al.* (U.S. Pat. No. 6,514,948, "Raz"), and Schwartz *et al.* (WO 98/55495, "Schwartz"). Applicants respectfully traverse this rejection and, as presented below, respectfully submit that a *prima facie* case of obviousness has not been established.

The claimed invention is directed to methods of delaying development and reducing severity of a lesion associated with papillomavirus infection in a human comprising administering an ISS-containing polynucleotide composition to a papillomavirus-associated lesion in the absence of administration of a papillomavirus antigen. Claim 1 is directed a method of delaying development of a lesion associated with papillomavirus infection through administration of the claimed ISS-containing polynucleotide to an individual exposed to papillomavirus. Claim 9 is directed to a method of reducing severity of a lesion associated with papillomavirus infection through administration of the claimed ISS-containing polynucleotide to an infected individual.

As acknowledged with the withdrawal of the previous obviousness rejection, the Office does not find the claimed invention obvious in view of the combination of Beutner, Bauman, and Yamamoto.[2] The Examiner bases the outstanding rejection on the combination of Beutner, Bauman, and Yamamoto further in view of either Raz or Schwartz and asserts that "the teachings of Raz and Schwartz references makes up to any deficiencies in the teachings of Beutner, Bauman, and Yamamoto." Office Action, page 6.

A *prima facie* case of obviousness requires that there be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. MPEP §2143. If this criteria is not met, a *prima facie* case of obviousness has not been established. Applicants

[2] Office Action, pages 5-6.

respectfully submit that there is no motivation to combine or modify the teachings of Beutner, Bauman, and Yamamoto with that of either Raz or Schwartz, to arrive at the claimed invention.

Raz is directed to a method for enhancing an immune response by administering an immunostimulatory nucleotide sequence prior to antigen exposure. Raz states that the "method of the invention can be used for broad protection against subsequently encountered pathogens as well as subsequently administered antigens" (emphasis added).[3] Thus, Raz provides a method for enhancing an immune response in an individual by systemic administration of the immunostimulatory nucleotide sequence before exposure to a pathogen.

Further, Raz does not teach or suggest that the method taught therein is effective in treating a papillomavirus infection. Nor does Raz teach or suggest that administration of the claimed ISS-containing polynucleotide results in production of IFN-α, delaying development or reducing severity of a lesion associated with papillomavirus infection.

Beutner and Bauman are directed to treating an existing papillomavirus infection with administration of an agent; imiquimod in the case of Beutner and IFN-α in the case of Bauman. Modifying Beutner and Bauman by administration of an immunostimulatory oligonucleotide to an individual before exposure to the virus as taught by Raz would be to change the principle of operation of Beutner and Bauman. Modifying Raz by administration of an agent to an individual after exposure to the virus as taught by Beutner and Bauman would be to change the principle of operation of Raz.

If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. M.P.E.P. §2143.01. One of skill in the art would have no motivation to combine the references or to modify the teachings of Beutner and Bauman with those of Raz. Thus, Applicants respectfully submit that a *prima facie* case of obviousness has not been established with regard to Beutner, Bauman, and Yamamoto further in view of Raz.

[3] Raz, col. 4, lines 17-20; see also, for example, col. 1, lines 15-17 and lines 44-52.

The Examiner states that Schwartz supports this rejection by recognizing "that the disclosed ISS had the ability to stimulate IFN-α, and therefore it was recognized in the art that, with respect to the IFN-α inducing activity, ISS were recognized equivalents of other adjuvants used to treat papillomavirus infection." Office Action, page 7. Applicants respectfully submit, however, that although Schwartz describes that administration of an ISS-containing polynucleotide and antigen can lead to an increase in the production of IFN-α, Schwartz does not teach or suggest that administration of an ISS-containing polynucleotide without antigen results in the production of IFN-α.[4] As noted, in the claimed invention, papillomavirus antigen is not administered in conjunction with the administration of the ISS-containing composition. One of skill in the art would have no motivation to combine the references or to modify the teachings of Beutner and Bauman with those of Schwartz. Thus, Applicants respectfully submit that a *prima facie* case of obviousness has not been established with regard to Beutner, Bauman, and Yamamoto further in view of Schwartz.

A *prima facie* case of obviousness requires that there must be a reasonable expectation of success and the reasonable expectation of success must be found in the prior art, not in applicant's disclosure. MPEP §2143. If this criteria is not met, a *prima facie* case of obviousness has not been established. Even if it is suggested that a motivation to combine the references exists, which Applicants decidedly do not, the combination of Beutner, Bauman, and Yamamoto with that of either Raz or Schwartz does not provide a reasonable expectation of success with regard to the claimed invention.

The Examiner states that a reasonable expectation of success exists because Bauman recognizes that IFN-α "was effective to treat papillomavirus infections" and that this "provides sufficient basis for those in the art to have a reasonable expectation of success in the use of an ISS, which also induces the production of this cytokine, to treat papillomavirus infections." Office Action, page 7.

Since the method of Raz is effective when the immunostimulatory oligonucleotide is administered before exposure to the pathogen, the combination of Raz with the primary references does not provide an reasonable expectation of success for the claimed invention. Since Schwartz

[4] See, for example, Schwartz, page 9, lines 3-10.

describes only the production of IFN-α when an ISS-containing polynucleotide is administered in conjunction with an antigen, the teachings of Schwartz do not support a reasonable expectation of success with regard to the claimed invention. In addition, Schwartz does not teach or suggest the administration of an ISS-containing polynucleotide for delaying development or reducing severity of a lesion associated with a papillomavirus infection, much less doing so without administration of a papillomavirus antigen. Thus, Applicants respectfully submit that a *prima facie* case of obviousness has not been established.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §103.

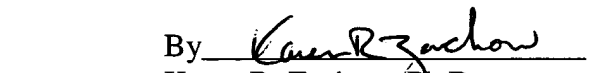
CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' representative at the telephone number below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 377882001300. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: March 15, 2005

Respectfully submitted,

By 

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